December 13, 2021

Via Regulations.gov

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20857

Re: Docket No. FDA-2020-N-1245: Drug Products Approved in Abbreviated New Drug Applications Before the Enactment of the Hatch-Waxman Amendments; Establishment of a Public Docket; Request for Comments, 86 Fed. Reg. 44,731 (Aug. 13, 2021).

To whom it may concern:

Teva Pharmaceuticals ("Teva" or "the Company") is pleased to provide the following response to the above-captioned *Federal Register* notice, which raises questions regarding the appropriate regulatory treatment of Abbreviated New Drug Applications ("ANDAs") that were approved prior to the enactment of the Hatch-Waxman Act ("PANDAs").

Teva and its affiliates manufacture and sell an array of generic medications, including many generic drugs that appear on the PANDA List FDA released alongside this docket. Given the breadth of Teva's portfolio of generic medicines—which are used to fill approximately one of every ten prescriptions in the United States—we believe that Teva is uniquely positioned to address the impact that subjecting PANDAs to the same requirements as New Drug Applications ("NDAs") would have on marketplace composition and, ultimately, on patients.

In a word, FDA's proposal would be disastrous. As we detail below using specific examples drawn from FDA's PANDA List, newly subjecting these ANDAs to the same requirements as full section 505(b) NDAs would ensure that sponsors withdraw many of these low-price products from the marketplace. The Agency's proposal already is forcing Teva to evaluate the potential market withdrawal of many products that appear on the PANDA List, and comments prepared by the Association for Accessible Medicines (the "AAM Comments") indicate that other generic manufacturers are likely doing so, as well. The reason is simple: For many products that appear on the PANDA List—including scores of affordable drugs that currently generate less than $100,000 in annual gross sales—it simply isn't rational to assume the onerous burdens that apply to full NDAs because the resulting costs likely would dwarf any return from continuing to market these low-cost products.

Reversing forty years of consistent and Congressionally sanctioned regulatory practice—under which PANDAs have been treated just like all other ANDAs—thus would fundamentally damage the competitive landscape. And consumers ultimately will pay the price. Several of the drugs on the PANDA List already appear on the Agency's Drug Shortage List; if these PANDAs are subjected to the same requirements as NDAs, that list is guaranteed to grow, leaving patients without reliable access to these important therapies. And where these products do remain available, there will be fewer versions on the market, less robust competition, and predictably higher prices. It hardly is far-fetched to imagine a repeat

of the Daraprim® fiasco—which, not coincidentally, involved what once had been a low-cost pre-Hatch-Waxman drug (albeit a genuine section 505(b) NDA product, not a PANDA).

For the reasons detailed at length in the AAM Comments, we do not believe FDA has the legal authority to subject these ANDA products to the same regulatory scheme that applies to genuine section 505(b) NDAs. To the extent FDA disagrees, however, Teva urges the Agency in the strongest possible terms to reconsider its ill-advised proposal to jettison a regulatory approach that FDA and Congress alike have embraced for generations.

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As the AAM Comments detail, PANDAs are ANDAs—not full section 505(b) NDAs—and, not surprisingly, have never been considered by Congress, FDA, or the industry as being subject to the same requirements as full section 505(b) NDAs. *See* AAM Comments at 3-7. The Agency's *Federal Register* notice acknowledges as much; it concedes, at least in passing, that Congress both defined PANDAs as ANDAs and made clear they should be treated just like post-Hatch-Waxman ANDAs when it passed the Generic Drug User Fee Act ("GDUFA"). 21 U.S.C. § 379j-41(1) (expressly defining the term "abbreviated new drug application" as including any "abbreviated new drug application submitted pursuant to regulations in effect prior to the implementation of the Drug Price Competition and Patent Term Restoration Act of 1984"). That alone should dissuade FDA from attempting to regulate PANDAs as though they are full section 505(b) NDAs; doing so would conflict with Congress's explicit recognition that PANDAs should not be subject to greater regulatory burdens than other ANDAs.

That legislative judgment did not arise in a vacuum. Instead, it ratified FDA's own longstanding recognition that PANDAs are ANDAs, not true section 505(b) NDAs. Despite the formalistic position advanced in the *Federal Register* notice—that PANDAs must be subject to the same requirements as section 505(b) NDAs because the pre-Hatch-Waxman Federal Food, Drug, and Cosmetic Act ("FDCA") only authorized the approval of section 505(b) NDAs, *see* 86 Fed. Reg. at 44732—the Agency repeatedly has refused to subject PANDAs to the same statutory and regulatory requirements as genuine section 505(b) NDAs, both before and after Hatch-Waxman's passage.

For example, prior to Hatch-Waxman's enactment in 1984, FDA routinely rejected the submission of PANDAs even though FDCA section 505(b) expressly authorized applicants to "file with the Secretary ***an application with respect to any drug***," 21 U.S.C. § 355(b) (1982) (emphasis added). *See* 48 Fed. Reg. 2751, 2752 (1983) (acknowledging that FDA refused to file more than 40 PANDAs between 1977 and 1983). That position would have been indefensible if PANDAs were legally indistinguishable from section 505(b) NDAs and therefore subject to the same rights and obligations as section 505(b) NDAs; if PANDAs really were section 505(b) NDAs, FDA could not have barred their Congressionally authorized submission. *Cf. Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120, 125 (D.C. Cir. 2006) ("We have previously rejected at *Chevron* step one the FDA's attempt to add to the statutory requirements for exclusivity.") (citing *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998)).

Consistent with its recognition that PANDAs are not genuine 505(b) applications—and thus that FDA could bar their filing despite Congress's explicit filing authorization—FDA in turn refused to grant aggrieved PANDA applicants administrative hearings under FDCA section 505(c), *see* 48 Fed. Reg 2751, 2752 (Jan. 21, 1983), even though that provision otherwise required FDA to afford any aggrieved section

505(b) NDA applicant a "hearing before the Secretary under subsection (d) on the question of whether such application is approvable." 21 U.S.C. § 355(c)(2) (1982); *id.* at §§ 355(d)(1), (4), (5) (1982) (authorizing FDA to reject a section 505(b) NDA where "the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use," where a given section 505(b) application otherwise "has insufficient information to determine whether such drug is safe for use," or where "the information submitted ... as part of the [section 505(b)] application and any other information before [FDA] with respect to the drug ... lack[s] substantial evidence that the drug will have the effect it purports or is represented to have").

That, too, would have been indefensible if PANDAs were legally indistinguishable from section 505(b) NDAs. Yet as FDA explained when it stripped PANDA applicants of the statutory rights Congress otherwise granted to ***all*** section 505(b) NDA sponsors, "[s]ection 505(c) of the act provides for an opportunity for hearing only on whether an application may be approved on the basis of the information submitted under section 505(b) of the act," and PANDAs—in stark contrast to section 505(b) NDAs—contained no such information because their submission instead was "based on agency-promulgated regulations" that imposed fundamentally different requirements from the data-based safety standards section 505(b) established and section 505(c) hearings were designed to address. *See* 48 Fed. Reg. at 2752. The recent *Federal Register* notice cannot be squared with the Agency's decades-old recognition that PANDAs were creatures of FDA's ANDA regulations, not section 505(b), and therefore outside the regulatory structure that applies to genuine section 505(b) NDAs.

Even after Hatch-Waxman's passage, FDA likewise maintained that ANDAs submitted under its pre-Hatch-Waxman ANDA regulations should be considered under section 505(j) of the statute—not under section 505(b). That made sense: As the AAM Comments explain, the whole point of the Hatch-Waxman Act was to validate (and, indeed, extend) the Agency's pre-Hatch-Waxman ANDA process—not draw lines between ANDAs submitted under the Agency's pre-Hatch-Waxman regulations and those submitted after Hatch-Waxman added section 505(j) to the statute. *See* AAM Comments at 5-6. And that is precisely how FDA has approached this issue ever since. When the Agency first proposed new FDCA-implementing regulations in 1989, it made this point expressly—explaining that ANDAs submitted under its pre-Hatch-Waxman regulations "will be treated as submitted under section 505(j) of the act rather than under section 505(b) of the act." 54 Fed. Reg. 28872, 28890 (July 10, 1989).

It would be hard to imagine a more explicit rejection of the position that FDA now suggests, which of course is why the Agency's *Federal Register* notice concedes that subjecting PANDAs to the section 505(b) NDA requirements at this late date "could be a change in practice" that conflicts with PANDA sponsors' long-held understanding that "the requirements that apply to 505(j) ANDA holders to also apply to their applications." 86 Fed. Reg. at 44,735. Indeed, it is more than just a "change in practice." Reversing course now would scramble generations of agency regulations, policies, and precedents that Congress expressly ratified when it passed GDUFA and that PANDA sponsors have relied upon for decades.

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The above is reason enough to withdraw the *Federal Register* notice and reiterate what both Congress and FDA consistently have maintained until now: that PANDAs are ANDAs, with the same rights and subject

to the same obligations as all other ANDAs. To the extent FDA nonetheless believes it has the legal authority to proceed, however, Teva urges the Agency to reconsider such an approach. As the AAM Comments again explain, PANDA sponsors are ill-equipped to assume the post-marketing obligations that apply to section 505(b) NDAs because they lack access to the underlying clinical trial data and safety/effectiveness analyses that FDA relied upon to approve their PANDAs (including the labeling for those PANDAs) in the first instance. AAM Comments at 2-3, 9-10.

Indeed, it is not clear how PANDA sponsors could be expected to comply with post-marketing requirements that plainly were designed with full section 505(b) NDAs in mind. For example, certain sections of an NDA product's previously approved labeling can be altered under the Changes Being Effected ("CBE") regulation only if, among other requirements, the NDA sponsor has "newly acquired information," 21 C.F.R. § 314.70(c)(6)(iii)(A), which is defined as "data, analyses or other information ***not previously submitted to the Agency***" that "reveal risks of a different type or greater severity or frequency ***than previously included in submissions to FDA***." *Id.* § 314.3(b). Yet precisely because PANDAs were submitted under FDA's ANDA regulations—and not in accordance with the statutory requirements for section 505(b) NDAs—PANDAs did not include any risk-related information in the first instance; as the Agency's *Federal Register* notice again acknowledges, FDA's ANDA policy was predicated on FDA's prior determination (as published in a DESI notice) that such products would be safe and effective. 86 Fed. Reg. at 44,732.

That is why FDA's pre-Hatch-Waxman ANDA regulations expressly exempted PANDAs from the statutory and regulatory clinical trial requirements, and did not otherwise require applicants to submit independent drug safety data or assessments in their PANDAs (just as ANDA applicants today neither conduct such trials nor provide such assessments). *See* 21 C.F.R. § 130.4(f) (1971) (exempting PANDA applicants from the NDA-specific requirements to include an "[e]valuation of safety and effectiveness" and provide "[f]ull reports of preclinical investigations" and "[f]ull reports of clinical investigations" under 21 C.F.R. § 130.4(c)). Moreover, PANDA sponsors have no way of knowing what other data, analyses, or information previously were submitted to the Agency by the sponsor of the NDA product on which a PANDA's approval was based.

The fact that the CBE regulation contemplates that an applicant could make such comparisons—and indeed could do so persuasively enough to justify a label change—is a sure sign that PANDAs are not (and were never understood as being) subject to the CBE regulation's authorization for unilateral labeling changes regarding "newly acquired information." Without a baseline standard, derived from previously submitted clinical trial data and against which incoming data or information can be gauged, it is impossible for PANDA sponsors to make the comparative assessment required by the CBE regulation. Even if a PANDA sponsor received a postmarketing report of an adverse event that is not listed in the labeling for its drug, the PANDA sponsor could not determine if the adverse event was submitted previously to the Agency because its PANDA contained no clinical trial data and because the sponsor has no way of knowing (beyond what already is including in the product's FDA-approved labeling) what postmarketing reports previously were received by the NDA sponsor, submitted to FDA, or otherwise considered the Agency. Similarly, it is all but impossible for the PANDA sponsor to determine exactly what information FDA considered up to 60 years ago when it made the safety and effectiveness determination upon which submission of a PANDA was based.

It not only is impractical to subject PANDAs to requirements that never were intended to apply to these applications. The potential costs that could arise from imposing these requirements all but ensures that PANDA sponsors will be forced to withdraw their products from the market. As the Supreme Court has held, federal law preempts state-law warning and design tort claims against ANDA sponsors because ANDA sponsors cannot use the CBE regulation to unilaterally add new safety information to their product labeling (except to conform to the RLD's amended labeling, or as here, the updated labeling for a pre-1962 product listed in a DESI notice). *Mutual Pharm. Co. v. Bartlett*, 570 U.S. 472, (2013) ("[A]s this Court recognized just two Terms ago in *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011), federal law prohibits generic drug manufacturers from independently changing their drugs' labels."). Subjecting PANDAs to the same rules as section 505(b) NDAs likely would lead to new litigation against PANDA sponsors, even though (as set forth above) PANDA sponsors lack the data and information necessary to make the kinds of judgments on which CBE-0 changes depend. PANDA sponsors in turn would be forced to incur unnecessary and unanticipated litigation expenses in defending and dispensing with those claims, which have no factual or legal basis, but which are a possible result of the action described in the *Federal Register* notice.

For PANDA drugs in particular, that prospect is intolerable. Unlike blockbuster brand-name drugs that often generate hundreds of millions of dollars (and, increasingly, billions of dollars) in annual sales, PANDA products overwhelmingly tend to be low-cost, low-margin products. That hardly is surprising. Again, their analogues necessarily were approved ***before 1962*** and every single PANDA was, by definition, approved ***before 1984***. As far as we can tell, PANDAs invariably lack patent protection. Nearly 40 years after the last PANDA was approved, none is subject to a period of regulatory exclusivity. And given advances in medicine, most PANDAs either face robust competition from newer drugs or serve as niche (if nonetheless important) therapies.

For that reason, many (if not most) PANDA products generate less than $100,000 in gross annual sales for their sponsors, and the total market sales for many of these products (across all equivalent versions) is less than $10 million per year.[1] The portfolio of PANDA drugs held by Teva and its affiliates perfectly illustrates this point. Of the roughly 30 individual PANDA products that Teva and its affiliates currently market, the median annual gross sales total is roughly $650,000 per product, and ten of those PANDA products generate annual gross sales of less than $500,000—a fraction of the cost it can often take to defend even the most meritless lawsuit (irrespective of any corollary costs, like higher product liability premiums). Indeed, pre-trial discovery alone can cost millions of dollars per case. *See, e.g.*, Lawyers for Civil Justice *et al.*, *Litigation Cost Survey of Major Companies for Presentation to the Committee on Rules of Practice and Procedure, Judicial Conference of the United States*, at 15 (May 10-11, 2010) ("In 2008, average discovery costs were as high as $2.4 million and the average discovery cost over all reporting companies was well in excess of $600,000. [A]verage outside legal fees per case were $2.0 million.").

The upshot is straightforward: Because the cost of defending even a single, frivolous claim would dwarf any reasonably expected return from continuing to sell these products—in most cases, by orders of magnitude—PANDA sponsors will have no choice but to withdraw many of these products from sale.

[1] All data referenced herein is drawn from IQVIA and is based on rolling figures for the 12-month period that ended August 31, 2021, shortly after FDA published its *Federal Register* notice.

The consequences of subjecting PANDAs to the same obligations as section 505(b) NDAs in turn will reverberate through the healthcare system. Jettisoning FDA's longstanding recognition that PANDAs are ANDAs is almost certain to perpetuate existing drug shortages. Five of the PANDA products Teva currently markets already appear on the Agency's Drug Shortage List; eight are included on the World Health Organization's Model List of Essential Medicines (the "WHO List"). And among Teva's inactive (but not yet withdrawn or discontinued) PANDA products, five more appear on the Drug Shortage List, and three are on the WHO List. In light of the burdens that a possible regulatory reclassification of PANDAs would impose, Teva—which otherwise might be able to help address those shortages—would be in no position to do so.

Abandoning FDA's decades-long regulatory approach to PANDAs not only would perpetuate existing drug shortages; it is likely to cause new ones. Consider isoniazid tablets, a critical tuberculosis treatment, on the WHO List, which FDA's PANDA List indicates the Agency first approved (at least in PANDA form) in the early 1970s. *See* PANDA List at 7-8 (listing Teva-affiliated Barr Laboratories' ANDAs 080936 and 080937). Although the Agency's *Drugs @ FDA* website indicates that at least 30 isoniazid ANDAs have been approved during the past 50 years, nearly all of those ANDAs have been discontinued. It is obvious why: Despite total annual sales of more than 10 million units across all remaining sellers, IQVIA's data reflect that isoniazid generates just over $1.6 million per year in gross sales revenues—or roughly 16 cents per unit. Even so, Teva has continued to market this important medication, and its isoniazid products now account for more than 90 percent of all isoniazid sales (with Viatris and American Health Packaging running a very distant second and third). Teva's prospective withdrawal from the market would leave a vacuum, and it hardly is clear that either of the remaining sellers are positioned (or, given the opportunity costs, would attempt) to engineer a ten-fold increase in their current production rates—much less that they would maintain the negligible price of these products under the resulting duopoly conditions. Isoniazid could become the next Daraprim®.

Even outside the drug-shortage context, the likely withdrawal of PANDAs as a result of FDA's new proposal would erode the current competitive landscape and create opportunities for potentially significant price increases. Consider primidone, an antiepileptic treatment for seizures. Though IQVIA's data indicate that seven different companies recorded sales during the past year, the market currently is dominated by two sellers: Bausch Health, which markets a high-priced, NDA version (Mysoline®), and Amneal Pharmaceuticals, whose generic primidone products account for roughly 80 percent (~29 million units) of total annual primidone unit sales (~34 million units) at what appears, based on IQVIA's data, to be about one-half of one percent of Mysoline®'s per-unit cost (by our calculations, roughly ***23 cents*** per unit versus roughly ***45 dollars*** per unit).

Importantly, of the remaining ANDA versions, the third and fourth best-selling products are PANDAs: one held by Teva's affiliate Watson Laboratories and the other by Lannett Company. *See* PANDA List at 11 (listing Lannett's ANDA 084903 and Watson's ANDA 083551). Combined unit sales under these two PANDAs (~4.5 million units per year) in turn are nearly ten times greater than the remaining three generics' total combined sales (~530,000 units). It is not difficult to see what will happen if a prospective regulatory reclassification of PANDAs forces Teva and Lannett to withdraw their PANDA products from the market; Amneal would be left in virtually sole control of the market for generics, where it will face no serious competition from the other sellers whose combined unit sales amount to less than two percent of Amneal's current market share and who therefore cannot exert the competitive pricing pressure needed to

keep Amneal's prices so far below Bausch's apparent pricing for Mysoline®. Once again, it is far from clear that any of those companies is positioned to increase their production by orders of magnitude; at best, it would take years for them to fill the void, while consumers—quite literally—pay the price for the ill-advised change suggested in FDA's *Federal Register* notice.

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Needless to say, these outcomes are directly at odds with the animating purpose of the ANDA process. As the Agency's *Federal Register* notice acknowledges, FDA's pre-Hatch-Waxman ANDA policy and regulations were designed in the first instance to facilitate marketplace competition by establishing "a streamlined and more administratively efficient path to seek FDA approval" for generic drugs. 86 Fed. Reg. at 44,732 (citing 47 Fed. Reg. 46,622, 46,631-32 (October 19, 1982)). And Hatch-Waxman in turn sought both to validate and extend FDA's prior ANDA policy for the avowed purpose of "get[ting] generic drugs into the hands of patients at reasonable prices—fast," *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991), not to draw formalistic lines between the regulatory obligations applicable to ANDAs approved before Congress added subsection 505(j) to the statute and ANDAs approved afterward.

If adopted, the approach suggested in the *Federal Register* notice would upend that legacy—subjecting PANDAs to regulatory burdens that never were intended to apply to these products; effectively (if unintentionally) reducing patient access to valuable therapies that manufacturers like Teva can no longer risk providing; and reducing the marketplace competition that patients depend upon. Teva strenuously urges FDA to abandon this proposal and make clear, once again, what Congress, the Agency, and the industry have recognized for generations: that PANDAs are ANDAs, with the same rights and obligations as all other ANDAs.

Respectfully submitted,

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